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A. INTRODUCTION:

There is some evidence that pesticide exposure is a risk factor for prostate cancer. Some pesticides, classified as endocrine-disrupting chemicals (EDCs), can affect normal hormone function. Variations in hormone levels affect prostate cancer risk, since normal growth of the prostate gland is dependent on a critical balance of androgen levels. Pesticides may affect hormone function by mimicking hormones, affecting enzyme systems involved in hormone metabolism, or directly affecting the brain regions involved in hormone functioning. A possible involvement of pesticides in prostate carcinogenesis is suggested by findings among farmers in studies of occupation and prostate cancer. The overall association reported by recent meta-analyses of farming and prostate cancer report a summary relative risk of 1.1, but the majority of studies with relatively large numbers of subjects consistently showed excess relative risks of prostate cancer ranging from 1.06 to 5.0. This limited evidence may well be inconclusive because of the difficulty in measuring true pesticide exposure – all these studies relied on self-reported occupational exposure, resulting in bias towards the null, and the omission of non-occupational environmental exposures (e.g. residences downwind of application sites). A large-scale population-based case-control study in California's Central Valley, the nation's leading user of pesticides, simultaneously assessing genetic and environmental risk factors for prostate cancer in an ethnically-diverse population with varying occupational and residential exposures to pesticides would go a long way to further refining knowledge of prostate cancer etiology. However, the complexities of such a study warrant excellent pilot data. We have been evaluating for some time now the use of Pesticide Use Reporting (PUR) data, refined by additional data on land use, in a Geographical Information System (GIS) to obtain objective historical pesticide exposure estimates.

This project is a pilot case-control study of pesticide exposure and prostate cancer, hypothesizing that (1) attenuation of estimates of the relative risk of pesticide exposure and prostate cancer in the absence of full (residential and occupational) historical pesticide exposures is significant, and could explain null findings to date; (2) our proposed method of recruiting and approaching cases and controls to a large population-based case-control study will result in acceptable response rates, but our sample will be biased with respect to socioeconomic status, race, and disease characteristics – we will preferentially recruit higher SES, white males with localized disease; (3) We will be able to obtain sufficient DNA from mailed buccal swab kits to assess effect modification by known relevant genes, and have sufficient stored DNA to assess the impact of genes that may be discovered in future.

B. PROGRESS TOWARDS SPECIFIC AIMS.

Specific Aims outlined in the Statement of Work were:

1. show that **historical** residential and PUR/land use data provides substantial **reduction in exposure misclassification** in both prostate cancer cases and controls

compared to estimates based only on **current** residential addresses and PUR/land use data information alone

2. demonstrate the **feasibility** of conducting a case-control study of biochemical and environmental risk factors (especially pesticide exposure), susceptibility genes, and their interactions for prostate cancer in the Central Valley. In particular, we will demonstrate the feasibility of our **case selection method**, **control selection method**, and **methods of obtaining buccal DNA** for genetic hypotheses.

Accomplishments to date:

1. Development of the GIS for determining exposure to pesticides.

The process for estimating pesticide exposure in this study relies on combining data from California's Pesticide Use Registry (PUR) and land use (PLSS) data to determine the exact location of applied pesticides.

We developed an automated program for combining the PUR and PLSS data within a GIS – this automated process was custom programmed in ArcGIS, and can be updated with new PUR and PLSS data as they become available. It also allows us to use any historical residential data (e.g. from other case-control studies) and generate pesticide exposure estimates.

We are currently using this GIS in this project to determine pesticide exposures, and in other studies where pesticide exposures are required (e.g. an ongoing study of risk factors for breast cancer in the inhabitants of California's Central Valley).

2. Development of questionnaire

We developed, piloted and refined a questionnaire that ascertained prostate cancer risk factor information, as well as detailed historical residential data (to incorporate into the pesticide exposure assessment) and detailed information on in-home and occupational exposure to pesticides. This questionnaire hgas been used throughout the study, and will be available as a deliverable at the conclusion of the study.

3. Recruitment and interview of prostate cancer cases

Aim 2. was to demonstrate the feasibility of conducting a case-control study of biochemical and environmental risk factors (especially pesticide exposure), susceptibility genes, and their interactions for prostate cancer in the Central Valley. In particular, we wished to demonstrate the feasibility of our case selection method, and methods of obtaining buccal DNA for genetic hypotheses.

We estimated we would be able to obtain 60 cases and controls, and in fact have recruited and interviewed almost twice that number of cases and over 80 controls to date.

We analyzed the representativeness of the cases included in our study (the response rate, after removing those cases we had no contact information for, was 64% - which is high for this kind of study which did not use rapid case ascertainment – but tells us nothing of the probability that we included a biased sample of cases). The results are summarized in Table 3, which compares the cases we obtained from the population-based Central California Cancer Registry with the cases we were able to interview

('surveyed cases') and those finally included in the analysis above (those providing informed consent and saliva sample for DNA analyses).

Table 4: Comparison of Cases Identified in the Central Valley Cancer Registry with Cases Surveyed and Cases in the Final Analysis.

		Attempted cases		Surveyed cases		Analysis cases	
Prostate Cancer, N (%)		NH white	Hispanic	NH white	Hispanic	NH white	Hispanic
	60-64	81 (28.42)	54 (27.00)	34 (30.91)	12 (34.29)	29 (28.71)	6 (46.15)
Diagnosis	65-69	111 (38.95)	77 (38.50)	42 (38.18)	12 (34.29)	40 (39.60)	5 (38.46)
Age, y	70-74	93 (32.63)	69 (34.50)	34 (30.91)	11 (31.43)	32 (31.68)	2 (15.38)
Stage	IN SITU			0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	LOCALIZED	233 (81.75)	161 (80.50)	91 (82.73)	31 (88.57)	83 (82.18)	11 (84.62)
	REGIONAL, DIRECT EXTENSIONS ONLY	35 (12.28)	26 (13.00)	13 (11.82)	2 (5.71)	12 (11.88)	0 (0.00)
	REGIONAL, NODES ONLY	3 (1.05)	0 (0.00)	2 (1.82)	0 (0.00)	2 (1.98)	0 (0.00)
	REGIONAL, DIRECT EXTENSION AND NODES	2 (0.70)	3 (1.50)	2 (1.82)	1 (2.86)	2 (1.98)	1 (7.69)
	DISTANT METASTASES OR SYSTEMIC DISEASE (REMOTE)	7 (2.46)	7 (3.50)	1 (0.91)	1 (2.86)	1 (0.99)	1 (7.69)
	UNSTAGEABLE; UNKNOWN	4 (1.40)	3 (1.50)	1 (0.91)	0 (0.00)	1 (0.99)	0 (0.00)
	MISSING	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Birthplace	UNITED STATES	144 (50.53)	67 (33.50)	58 (52.73)	11 (31.43)	52 (51.49)	4 (30.77)
	OTHER	9 (3.16)	43 (21.50)	4 (3.64)	9 (25.71)	4 (3.96)	5 (38.46)
	MISSING	132 (46.32)	90 (45.00)	48 (43.64)	15 (42.86)	45 (44.55)	4 (30.77)
		285	200	110	35	101	13

While we expected that we would preferentially select cases with a lower stage disease and cases more likely to be younger, and with a birthplace in the U.S. (the former two affecting generalizablilty of general prostate cancer risk factor information, the latter affecting our lifetime estimates of pesticide exposure from residential history), we found instead that there were few, if any, differences between the population-based sample of cases, and those included in the final analysis. This leads us to conclude that our case-control method yields a relatively unbiased source of cases and controls for this study design. While the response rate in the Hispanic population was lower than among the non-Hispanic White population, this is a misleading figure because we only added Hispanic cases near the end of the study, and had less time to recruit them. The recruitment-time specific response rates were very similar in Hispanic and non-Hispanic white populations in this study.

Extracting DNA from saliva specimens

We used the Oragene saliva kit to obtain specimens from all participants. We mailed participants the kits, and they were returned to us by mail. Specimens were stored at room temperature for 1-3 weeks before being processed by the lab.

We quantified DNA yield from saliva specimens. The overall mean yield was 27,887 ng, with a minimum of 351 ng, a maximum of 127,367 ng. 57% of samples had greater than 20,000 ng.

4. Initial analyses of pesticide exposure and prostate cancer risk

We used our Pesticide Exposure Analysis Software (PEAS) tool to estimate lifetime and age-specific exposures to a variety of pesticides and herbicides using residential history information, and combined data from the California Pesticide Use Registry (PUR) and Land Use Information, both available for years from 1974 to 1999. We have previously described how the latter are combined to produce an accurate estimate of year-specific pesticide application in small geographical areas (Ritz and Rull). Our PEAS model combines PUR and LU data for each reported residence for the lifetime history of cases and controls.

We hypothesized that previous studies of prostate cancer and pesticide exposure that only considered exposures occurring at time of diagnosis would underestimate the true relationship due to (1) random misclassification (inaccurate estimation of exposure) resulting in bias towards the null (2) specifically underestimating exposure in cases only, resulting in a differential bias, but still with a net effect of bias towards the null.

In our initial analyses of these effects, we focused on the main pesticide groupings that have been shown to have relationships with prostate cancer, namely methyl bromide, captan, and simazine. Ongoing analyses are assessing other pesticides, and groupings of pesticides, such as organochlorines.

We calculated exposures for (1) diagnosis year only (2) life time (ie age 0 to age at diagnosis) – for this exposure, we assumed that year 1974 pesticide use continued back through time to the earliest year required (3) the period 1974 to 1999 only (the years for which PUR/LU data were available (4) accumulated exposures in the 10 years prior to diagnosis only (5) accumulated exposures in the 20 years prior to diagnosis only.

Mean exposure levels are summarized in Table 1.

Table 1: Mean exposure levels for key pesticides in cases and controls in California's Central Valley, 2005-6.

Annual Exposure (in pounds)	Mean	Std Err	Count
Methyl Bromide			
DX Year	36.51	13.20	179
Life time	18.29	4.34	192
1974 - 1999	28.94	6.47	177
10 years prior to DX	11.18	3.32	173
15 years prior to DX	4.98	1.65	162

Captan			
DX Year	2.48	1.04	179
Life time	0.94	0.23	192
1974 - 1999	1.46	0.35	177
10 years prior to DX	0.91	0.28	173
15 years prior to DX	0.74	0.19	162
Simazine			
DX Year	5.13	1.48	179
Life time	1.98	0.38	192
1974 - 1999	2.49	0.73	178
10 years prior to DX	1.29	0.24	174
15 years prior to DX	1.14	0.27	162

We then calculated crude odds ratios (ORs) and ORs adjusted for age, race, and home pesticide use (yes/no for ever used pesticides in the home). These results are outlined in Tables 2a-c for each of the exposure time periods noted above, which also provide 95% CIs for effect estimates, and p-values for the difference between exposure levels. Because the distribution of exposure was skewed, we provide both an estimate of the relative risk for any exposure (ie >0), and for two levels of exposure (medium and high, depending on the distribution of exposure), both compared to 0 exposure as a baseline.

Table 2a. Relative risk estimates for prostate cancer with exposure to Methyl Bromide in California's Central Valley, 2005-2006.

Methyl Bromide										
Exposure Type	Exposure frequency		Crude				Adjusted			
	Control	Case	OR***	Lower	Upper	p - value	OR**	Lower	Upper	p - value
DX Year Exposure										
Missing	13	8	-	-	-		-	-	-	
0*	66	93	1.00	-	-		1.00	-	-	
>0	7	13	1.32	0.50	3.48	0.58	1.19	0.43	3.31	0.73
0-3	2	3	1.06	0.17	6.55	0.83	0.78	0.12	5.02	0.82
3+	5	10	1.42	0.46	4.35		1.39	0.43	4.52	
Life Time										
Missing	4	4	-	-	-		-	-	-	
0	45	53	1.00	-	-		1.00	-	-	
>0	37	57	1.31	0.74	2.32	0.36	1.21	0.65	2.26	0.54
0-3	12	29	2.05	0.94	4.48	0.15	1.57	0.69	3.59	0.52
3+	25	28	0.95	0.49	1.86		1.00	0.48	2.07	
1974 - 1999										
Missing	8	15	-	-	-		-	-	-	
0	42	43	1.00	-	-		1.00	-	-	
>0	36	56	1.52	0.84	2.76	0.17	1.39	0.73	2.66	0.32
0-3	9	26	2.82	1.18	6.73	0.06	2.16	0.87	5.38	0.24

3+	27	30	1.09	0.55	2.12		1.08	0.52	2.24	
10 year prior DX										
Missing	10	17	-	-	-		-	-	-	
0	45	50	1.00	-	-		1.00	-	-	
>0	31	47	1.36	0.74	2.50	0.32	1.34	0.69	2.60	0.39
0-3	17	28	1.48	0.72	3.06	0.56	1.30	0.59	2.84	0.69
3+	14	19	1.22	0.55	2.72		1.39	0.57	3.38	
15 year prior DX										
Missing	14	24	-	-	-		-	-	-	
0	43	47	1.00	-	-		1.00	-	-	
>0	29	43	1.36	0.72	2.54	0.34	1.28	0.65	2.54	0.47
0-3	17	29	1.56	0.75	3.23	0.48	1.52	0.69	3.36	0.54
3+	12	14	1.07	0.44	2.56		0.96	0.37	2.47	

* Exposure measured in pounds
** Adjusted for age, race and home pesticide use
*** Baseline is 0 exposure

Table 2b. Relative risk estimates for prostate cancer with exposure to Captan in California's Central Valley, 2005-2006.

Captan											
Exposure Type		Exposure frequency		Crude				Adjusted			
		Control	Case	OR***	Lower	Upper	p - value	OR**	Lower	Upper	p - value
DX Year Exposure											
	Missing	13	8	-	-	-		-	-	-	
	0*	69	94	1.00	-	-		1.00	-	-	
	>0	4	12	2.20	0.68	7.12	0.19	1.89	0.56	6.37	0.30
	0-0.5	0	1	-	-	-	0.51	-	-	-	0.67
	0.5+	4	11	2.02	0.62	6.61		1.74	0.51	5.96	
Life Time											
	Missing	4	4	-	-	-		-	-	-	
	0	55	71	1.00	-	-		1.00	-	-	
	>0	27	39	1.12	0.61	2.05	0.72	1.20	0.63	2.30	0.58
	0-0.5	15	13	0.67	0.30	1.53	0.20	0.90	0.37	2.21	0.58
	0.5+	12	26	1.68	0.78	3.62		1.48	0.66	3.33	
1974 - 1999											
	Missing	8	15	-	-	-		-	-	-	
	0	51	62	1.00	-	-		1.00	-	-	
	>0	27	37	1.13	0.61	2.09	0.70	1.17	0.60	2.29	0.64

	0-0.5	10	9	0.74	0.28	1.96	0.51	0.96	0.33	2.81	0.81
	0.5+	17	28	1.35	0.67	2.75		1.27	0.60	2.72	
10 year prior DX											
	Missing	10	17	-	-	-		-	-	-	
	0	51	63	1.00	-	-		1.00	-	-	
	>0	25	34	1.10	0.58	2.08	0.77	1.16	0.58	2.31	0.68
	0-0.5	13	11	0.68	0.28	1.66	0.31	0.99	0.37	2.67	0.84
	0.5+	12	23	1.55	0.70	3.42		1.28	0.56	2.96	
15 year prior DX											
	Missing	14	24	-	-	-		-	-	-	
	0	50	58	1.00	-	-		1.00	-	-	
	>0	22	32	1.25	0.65	2.43	0.50	1.25	0.61	2.56	0.54
	0-0.5	12	11	0.79	0.32	1.95	0.28	1.07	0.39	2.94	0.76
	0.5+	10	21	1.81	0.78	4.20		1.40	0.58	3.38	

* Exposure measured in pounds

** Adjusted for age, race and home pesticide use

*** Baseline is 0 exposure

Table 2c. Relative risk estimates for prostate cancer with exposure to Methyl Bromide in California's Central Valley, 2005-2006.

Simazine											
Exposure Type		Exposure frequency		Crude				Adjusted			
		Control	Case	OR***	Lower	Upper	p - value	OR**	Lower	Upper	p - value
DX Year Exposure											
	Missing	13	8	-	-	-		-	-	-	
	0*	56	82	1.00	-	-		1.00	-	-	
	>0	17	24	0.96	0.47	1.96	0.92	1.02	0.48	2.18	0.95
	0-3	7	8	0.78	0.27	2.27	0.87	0.93	0.29	2.97	0.98
	3+	10	16	1.09	0.46	2.58		1.08	0.43	2.69	
Life Time											
	Missing	4	4	-	-	-		-	-	-	
	0	40	59	1.00	-	-		1.00	-	-	
	>0	42	51	0.82	0.46	1.46	0.51	0.77	0.41	1.42	0.40
	0-3	29	29	0.68	0.35	1.30	0.39	0.62	0.30	1.26	0.34
	3+	13	22	1.15	0.52	2.54		1.08	0.46	2.52	
1974 - 1999											
	Missing	7	15	-	-	-		-	-	-	
	0	38	55	1.00	-	-		1.00	-	-	

	>0	41	44	0.74	0.41	1.34	0.32	0.69	0.36	1.30	0.25
	0-3	30	27	0.62	0.32	1.21	0.31	0.56	0.28	1.16	0.26
	3+	11	17	1.07	0.45	2.53		1.02	0.40	2.56	
10 year prior DX											
	Missing	9	17	-	-	-		-	-	-	
	0	39	53	1.00	-	-		1.00	-	-	
	>0	38	44	0.85	0.47	1.55	0.60	0.73	0.38	1.42	0.36
	0-3	28	27	0.71	0.36	1.39	0.43	0.64	0.31	1.34	0.48
	3+	10	17	1.25	0.52	3.03		0.95	0.37	2.44	
15 year prior DX											
	Missing	14	24	-	-	-		-	-	-	
	0	42	51	1.00	-	-		1.00	-	-	
	>0	30	39	1.07	0.57	2.00	0.83	0.87	0.44	1.72	0.69
	0-3	22	27	1.01	0.50	2.03	0.91	0.84	0.40	1.80	0.91
	3+	8	12	1.24	0.46	3.30		0.94	0.33	2.69	

* Exposure measured in pounds
** Adjusted for age, race and home pesticide use
*** Baseline is 0 exposure

5. Recruitment of an unbiased sample of control subjects by visiting residential tax assessor parcel units in the study area.

We recently initiated home visits to recruit control subjects, as outlined in the Statement of Work. To date we have made 3 field trips into the Central Valley, each consisting of 3 days work by 2 teams of 2 interviewers. Key characteristics of this effort are:

- We have visited 213 households
- We have recruited 14 control subjects, who are in the process of being interviewed
- We have developed software for a handheld computer (PDA) with a built in GPS device that also validates the location of residential parcels (for future validation of residential history in our GIS) – this PDA is also used as the primary data collection tool for enumerating households and collecting baseline eligibility data for controls.

None of these controls occur in the above data, because at the time of writing this annual report, they have not yet completed interviews and study materials.

6. Continuation into Year 2.

- We will continue to recruit and interview cases to increase the sample size and refine the accuracy of the estimates of pesticide exposure's impact on prostate cancer.
- We will continue recruiting control subjects with our home visit protocol, and compare the controls recruited using this method to those found by phone contact, hypothesizing that the home visit control subjects will be a more representative sample of the underlying population. We will compare controls to the underlying population in two ways: (1) by comparing the control demographics (age, race, SES) to census data from the census tracts from which they were obtained; (2) by comparing the pesticide exposures in our PEAS model for controls to the average values for all areas under study, to determine if the selected controls had differing pesticide exposures than the underlying population (resulting in biased exposure estimates). In both cases we will quantify the potential bias.
- We will continue analyses of other pesticides and classes of pesticides.

C. KEY RESEARCH ACCOMPLISHMENTS:

Despite the fact that we are still in the process of collecting data, results to date appear to clearly show:

- Different estimates of relative risk are obtained when considering only diagnosis year exposures compared to lifetime exposures. However, these do not always result in a bias towards the null: the effect is pesticide-specific, which presumably is a result of the variation in application of pesticides over time. Pesticides that were more commonly applied recently will be affected differently from those more commonly applied decades ago.
- There appears to be an increased risk of prostate cancer associated with exposure to methyl bromide and captan, but not simazine. These results are in agreement with studies of occupational exposure to pesticides where exposure levels far exceed those to be expected in the residential environment, which we have measured here. No 95% CIs excluded 1.0, so these results must be heeded with caution, but require verification with a larger sample size.

With respect to Aim 2, it appears that our method of conducting a case-control study of prostate cancer risk factors in California's Central Valley will likely result in:

- An unbiased sample of cases
- Sufficient DNA for multiple SNPs
- A more accurate method for assessing ambient pesticide exposure than has been previously utilized.

When expanding this study to a full scale case-control study, we should:

- Obtain and process data from 2000 onwards from PUR and LUI (currently available)

- Design a follow-up process to immediately quantify DNA yield in specimens and return to the participant and ask for another specimen if the yield is below 10,000 ng

D. REPORTABLE OUTCOMES:

- The questionnaire used in this study was adapted from those used elsewhere, but will be made available online at the time of publication of our report of this project (particularly the questionnaire on residential history, which is central to the exposure analysis algorithm).
- The PEAS software was developed during this study, and is available from the PI (Cockburn@usc.edu). Currently it is on a shared volume on our server, and is not made openly available because the documentation regarding its use is not complete. However, we will complete that documentation in the near future and make it publicly available. To date, the software has been used under supervision of the PI for 3 additional studies of pesticide exposure in the Central Valley.
- Manuscripts outlining the automation of the PEAS process are in process.
- Other manuscripts currently being written include the following topics:
    - Comparison of DX address exposure and exposures using lifetime residential history in case-control data. Assess bias in considering only DX exposure, and build model of appropriate time sequence of exposure (i.e. time between exposure and DX, as opposed to age-specific exposure or total cumulative exposure). Aim is to come up with an exposure matrix that is biologically meaningful for specific pathways hypothesized. Compare mean exposures and resulting relative risks: DX-only exposure versus lifetime with known residential history:Versus age-specific exposure: Versus cumulative exposure (Age-weighted)
    - What is the effect of missing residential history data on residential history of pesticide exposure? Use case-control data to test the effect of various missing data imputation models to fill in holes:

        - Impact on lifetime versus age-specific, versus prior-to-DX specific exposures

        - Also analyze impact of missing pesticide exposure data (1970-99 versus other times)

        - Consider specific impacts of missing data from migrant populations (we know where the people missing pesticide exposure lived)

    - Why is the dose-response with pesticide exposure non-monotonic?

        - First, statistical test to show that it is non-monotonic

        - Then show that it is not just a function of the cut points used

        - Interaction with another confounder (varies by disease?) – versus competing risks, versus threshold effect.

E. CONCLUSION:

While this study is still ongoing, we believe we will be able to provide evidence that pesticide exposures appear to be strong risk factors for prostate cancer.

This study will ultimately be slightly limited by sample size, but it's purpose was to provide pilot data to justify a full scale case-control study of pesticide exposure in the development of prostate cancer. We believe that our preliminary results argue strongly for the need for a large-scale case-control study of the impact of pesticide exposures on prostate cancer.

If indeed pesticide exposure is associated with prostate cancer, the following should be considered:

- Ambient exposure to pesticides (i.e. exposure at residence, not occupational exposure) might explain increased risk of prostate cancer in certain geographical groups
- The impact of exogenous hormone exposure on prostate cancer might be substantial
- More research is required to determine what mechanisms cause pesticides to increase of prostate cancers – while these are presumably related to the hormone-mimicking affects of some pesticides, the exact mechanism, and therefore a means of prevention of prostate cancer, remain unknown.

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